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FORM PTO-1390 (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: CRF D-2165

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/554604

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US98/25206	7 December 1998	17 December 1997

TITLE OF INVENTION: CYCLOOXYGENASE-2 INHIBITION

APPLICANT(S) FOR DO/EO/US: ANDREW J. DANNENBERG

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [X] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [X] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information:
    (1) WO 99/30721
    (2) PCT/IB/332
    (3) PCT/IPEA/402

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U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/554604	PCT/US98/25206	CRF D-2165

17. [X] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

	CALCULATIONS PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$970.00**	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$840.00**	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$760.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$670.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$96.00**	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 670
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	16 - 20 =	NONE	X **$18.00**	$
Independent claims	3 - 3 =	NONE	X **$78.00**	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$260.00**	$
TOTAL OF ABOVE CALCULATIONS =				$
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).				$ 335
SUBTOTAL =				$ 335
Processing fee of **$130.00** for furnishing the English translation later than [ ]20 [ ]30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$
TOTAL NATIONAL FEE =				$
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 40
TOTAL FEES ENCLOSED =				$ 375
			Amount to be: refunded	$
			charged	$

a. [X] A check in the amount of $ 375.00 to cover the above fees is enclosed. (Check NO. 14768)

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 10-1213. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO.

Eric S. Spector
JONES, TULLAR & COOPER, P.C.
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Arlington, VA 22202

703-415-1500

SIGNATURE:

Eric S. Spector
NAME

22495
REGISTRATION NUMBER

Applicant or Patentee: Andrew J. Dannenberg
Filed or Issued: May 31, 2000
Title: CYCLOOXYGENASE-2 INHIBITION
Attorney's Docket No.: CRF D-2165

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) & 1.27(d)) -- NONPROFIT ORGANIZATION

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

NAME OF NONPROFIT ORGANIZATION **Cornell Research Foundation, Inc.**

ADDRESS OF NONPROFIT ORGANIZATION **20 Thornwood Drive, Suite 105, Ithaca, NY 14850**

TYPE OF NONPROFIT ORGANIZATION

*■ UNIVERSITY OR OTHER INSTITUTION OF HIGHER EDUCATION

☐ TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 U.S.C. 501(a) and 501 (c)(3))

☐ NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA

(NAME OF STATE _____)

(CITATION OF STATUTE _____)

☐ WOULD QUALIFY AS TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 U.S.C. 501(a) and 501(c)(3)) IF LOCATED IN THE UNITED STATES OF AMERICA

☐ WOULD QUALIFY AS A NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA IF LOCATED IN THE UNITED STATES OF AMERICA

(NAME OF STATE _____)

(CITATION OF STATUTE _____)

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 37 CFR 1.9(e) for purposes of paying reduced fees to the United States Patent and Trademark Office regarding the invention entitled CYCLOOXYGENASE-2 INHIBITION by inventors ANDREW J. DANNENBERG

described in:

☒ the specification filed herewith.

☐ application serial no. _____, filed _____.

☐ patent no. _____, issued _____.

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization regarding the above identified invention.

If the rights held by the nonprofit organization are not exclusive, each individual, concern or organization having rights in the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

*NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME
ADDRESS
☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

NAME
ADDRESS
☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

NAME
ADDRESS
☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING **James A. Severson**

TITLE IN ORGANIZATION OF PERSON SIGNING **President**

ADDRESS OF PERSON SIGNING **20 Thornwood Drive, Suite 105, and Ithaca, New York 14850**

SIGNATURE James A. Severson DATE May 31, 2000

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CYCLOOXYGENASE-2 INHIBITION

Technical Field

One invention herein is directed to an expansion of the use of selective inhibitors of cyclooxygenase-2. A different invention herein is directed to cyclooxygenase-2 inhibitors with antioxidant properties.

Background of the Invention

Substantial research is currently being carried out to develop selective inhibitors of cyclooxygenase-2, i.e., agents which selectively inhibit cyclooxygenase-2 in preference to cyclooxygenase-1, so as to obtain the anti-inflammatory effect of cyclooxygenase-2 inhibition without the gastrointestinal side effects, e.g., peptic ulcer disease, that occur when cyclooxygenase-1 is also inhibited. Commonly used nonsteroidal anti-inflammatory drugs inhibit both cyclooxygenase-2 and cyclooxygenase-1, and the aforementioned side effects detract from their usefulness.

The focus of the research has been on synthesis of new compounds providing selective inhibition of cyclooxygenase-2 for use for treating certain inflammatory conditions, especially arthritis. The focus has not been on developing new methods of treatment, i.e., on treating conditions not heretofore considered as appropriately treatable with cyclooxygenase-2 inhibitors. The focus has not been on developing compounds with desirable functions in addition to enzyme inhibition.

Heretofore, it was considered that cyclooxygenase inhibitors could cause liver injury and for that reason liver disease was not considered as one of the conditions that was treatable by selective inhibitors of cyclooxygenase-2.

Summary of the Invention

One embodiment herein, sometimes referred to hereinafter as the first embodiment herein, is directed to a method of treating a patient with liver disease

comprising administering to said patient a cyclooxygenase-2 inhibiting amount of a selective inhibitor of cyclooxygenase-2. Most liver diseases are treated with minimal success. There is no effective treatment for alcoholic liver injury. Although chronic hepatitis C affects millions of individuals, interferon therapy is effective in eradicating the virus in a relatively small percentage of patients, and in patients where the virus is not eradicated, the condition can progress to cirrhosis requiring liver transplantation. Invention in the method of treatment herein resides in the realization that the anti-inflammatory properties of selective cyclooxygenase-2 inhibitors will provide a net benefit in treating liver disease and the only effective treatment in many cases. This represents a major advance. Even considering just the ability to delay the progression of cirrhosis, the aforedescribed treatment method has enormous clinical implications.

A second embodiment herein is directed to a method of treating a patient with a virus-caused liver disease comprising administering to said patient a cyclooxygenase-2 inhibiting amount of a selective inhibitor of cyclooxygenase-2 and therapeutic amount(s) of anti-viral drug(s) where the cyclooxygenase-2 inhibitor is an adjunct to anti-viral therapy to increase the effectiveness thereof. In this embodiment, the treatment with a selective inhibitor of cyclooxygenase-2 is considered to cause a decrease in the synthesis of immunosuppressive eicosanoids, thereby augmenting anti-viral therapy.

A third embodiment herein is directed to selective inhibitor of cyclooxygenase-2 which directly inhibits the enzyme cyclooxygenase-2 and which also inhibits the synthesis of the cyclooxygenase-2 protein and which has antioxidant properties.

The term "selective inhibitor of cyclooxygenase-2" is used herein to mean compound which selectively inhibits cyclooxygenase-2 in preference to cyclooxygenase-1 and particularly compound for which the ratio of the IC_{50} concentration (concentration inhibiting 50% of activity) for cyclooxygenase-1 to the IC_{50} concentration for cyclooxygenase-2 is greater than 1. Such ratio is readily determined by assaying for cyclooxygenase-2 activity and assaying for cyclooxygenase-1 activity by the methods set forth at column 39, line 55 - column 40,

line 36 of Talley et al. U.S. Patent No. 5,633,272, which is incorporated herein by reference, and from the resulting data obtaining a ratio of IC_{50}s.

Detailed Description

We turn now to the embodiment herein directed to a method of treating a patient with a liver disease comprising administering to said patient a cyclooxygenase-2 inhibiting amount of a selective inhibitor of cyclooxygenase-2.

The liver diseases treated herein comprise inflammatory liver disorders and include, for example, chronic viral hepatitis B, chronic viral hepatitis C, alcoholic liver injury, primary biliary cirrhosis, autoimmune hepatitis, nonalcoholic steatohepatitis, and liver transplant rejection.

The selective inhibitors of cyclooxygenase-2 are preferably those where the ratio of the IC_{50} concentration for cyclooxygenase-1 to the IC_{50} concentration for cyclooxygenase-2 is 5 or more, very preferably 100 or more.

Selective inhibitors of cyclooxygenase-2 include the following compounds:

(1) 4-[5-(4-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(2) 4-[5-(4-Bromophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(3) 4-[5-(3-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(4) 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(5) 4-[5-(2-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(6) 4-[5-(4-Trifluoromethylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(7) 4-[5-(4-Fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(8) 4-[5-Phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(9) 4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(10) 4-[5-(4-Trifluoromethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(11) 4-[5-(2-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(12) 4-[5-(4-Chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(13) 4-[4-(Aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazol-3-carboxylate

(14) 4-[4-(Aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1H-pyrazol-3-carboxamide

(15) 4-[5-(4-[Methylthio]phenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(16) 4-[5-(4-[Methylsulfonyl]phenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(17) 4-[5-(2,4-[Difluoro]phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(18) 4-[5-(2,6-[Difluoro]phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(19) 4-[5-(4-Cyanophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(20) 4-[5-(4-Chlorophenyl)-3-(heptafluoropropyl)-1H-pyrazol-1-yl]benzenesulfonamide

(21) 4-[5-(4-Chlorophenyl)-3-(chloro-difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(22) 4-[5-(4-Chlorophenyl)-3-(pentafluoroethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(23) 4-[5-(4-Biphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(24) 4-[5-(4-Pyrazinyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(25) 4-[5-(5-Chloro-2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(26) 4-[5-(4-Morpholino)phenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(27) 4-[5-(1-Cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(28) 4-[5-(5-Bromo-2-thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(29) 4-[5-(4-Thienyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(30) 4-[5-(4-[Trifluoromethyl]phenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(31) 4-[5-(3,4-Dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(32) 4-[5-(2,4-Dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

(33) 4-[5-Phenyl-3-(3-hydroxypropyl)-1H-pyrazol-1-yl]benzenesulfonamide

(34) 4-[5-(4-Fluorophenyl)-3-(3-hydroxypropyl)-1H-pyrazol-1-yl]benzenesulfonamide

(35) 4-[4-(Aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1H-pyrazole]-3-propanoic acid

(36) 4,5-Dihydro-4-[3-trifluoromethyl]-1H-benz[g]indazol-1-yl]benzenesulfonamide

(37) 4-[5-(4-Chlorophenyl)-4-chloro-1H-pyrazol-1-yl]benzenesulfonamide

(38) 4-[5-(4-Chlorophenyl)-3-(trifluoromethyl)-4-chloro-1H-pyrazol-1-yl]benzenesulfonamide

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(39) 4-[1-(4-Fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide

(40) 1-(2,4,6-Trichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid

(41) 1-(2,6-dichlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetic acid

(42) 3-(4-(Aminosulfonyl)phenyl)-2-(4-fluorophenyl)-5-(2-hydroxy-2-propyl)thiophene

(43) 3-(4-(Aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene

(44) 3-(4-(Aminosulfonyl)phenyl)-2-(4-fluorophenyl)-5-(2-propyl)thiophene

(45) 3-(4-(Aminosulfonyl)phenyl)-2-cyclohexylthiophene

(46) 5-(4-Carboxyphenyl)-4-(4-(methylsulfonyl)phenyl) thiophene-2-carboxylic acid

(47) 4-(4-Fluorophenyl)-2-methyl-5-(4-(methylsulfonyl) phenyl)thiazole

(48) 2-(4-Fluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopenten-1-one

(49) 4-(4-(Methylsulfonyl)phenyl-5-(4-fluorophenyl)-isothiazole

(50) 3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl-2-(5H)-furanone

(51) 3-(4-Fluorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(2H)-furanone

(52) 3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan

(53) 5,5-Dimethyl-3-(4-fluorophenyl)-4-(4-methylsulfonyl-phenyl)-2-(5H)furanone

(54) 2-((4-Aminosulfonyl)phenyl)-3-(4-fluorophenyl)thiophene

(55) 3-(2,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(56) 3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(57) 3-(2,6-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(58) 3-(2,5-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(59) 3-(3,5-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(60) 3-(4-Bromophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(61) 3-(4-Chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(62) 3-(4-Methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(63) 3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(64) 3-(2-Chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(65) 3-(2-Bromo-4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(66) 3-(2-Bromo-4-Chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(67) 3-(4-Chloro-2-fluorophenyl)-4-(4-(methylsulfonyl) phenyl)-2-(5H)-furanone

(68) 3-(3-Bromo-4-fluorophenyl)-4-(4-(methylsulfonyl) phenyl)-2-(5H)-furanone

(69) 3-(3-Chlorophenyl)-4-(4-(methylsulfonyl) phenyl)-2-(5H)-furanone

(70) 3-(2-Chloro-4-fluorophenyl)-4-(4-(methylsulfonyl) phenyl)-2-(5H)-furanone

(71) 3-(2,4-Dichlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(72) 3-(3,4-Dichlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(73) 3-(2,6-Dichlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(74) 3-(3-Chloro-4-fluorophenyl)-4-(4-(methylsulfonyl) phenyl)-2-(5H)-furanone

(75) 3-(4-Trifluoromethylphenyl)-4-(4-(methylsulfonyl) phenyl)-2-(5H)-furanone

(76) 3-(3-Fluoro-4-methoxyphenyl)-4-(4-(methylsulfonyl) phenyl)-2-(5H)-furanone

(77) 3-(3-Chloro-4-methoxyphenyl)-4-(4-(methylsulfonyl) phenyl)-2-(5H)-furanone

(78) 3-(3-Bromo-4-methoxyphenyl)-4-(4-(methylsulfonyl) phenyl)-2-(5H)-furanone

(79) 3-(2-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(80) 3-(4-Methylthiophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(81) 3-(3-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(82) 3-(2-Chloro-6-fluorophenyl)-4-(4-(methylsulfonyl) phenyl)-2-(5H)-furanone

(83) 3-(3-Bromo-4-methylphenyl)-4-(4-(methylsulfonyl) phenyl)-2-(5H)-furanone

(84) 3-(4-Bromo-2-fluorophenyl)-4-(4-(methylsulfonyl) phenyl)-2-(5H)-furanone

(85) 3-(3,4-Dibromophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(86) 3-(4-Chloro-3-fluorophenyl)-4-(4-(methylsulfonyl) phenyl)-2-(5H)-furanone

(87) 3-(4-Bromo-3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(88) 3-(4-Bromo-2-chlorophenyl)-4-(4-(methylsulfonyl) phenyl)-2-(5H)-furanone

(89) 3-(2-Naphthyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(90) 3-(7-Quinolinyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

(91) 3-(3,4-Dichlorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(2H)-furanone

(92) 3-(3,4-Dichlorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(2H)-furanone

(93) 3-(3,4-Dichlorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(2H)-furanone

(94) 3-(3-Bromo-4-methoxyphenyl)-4-(4-(aminosulfonyl) phenyl)-2-(2H)-furanone

(95) 3-(4-(Methylsulfonyl)phenyl)-2-phenylbenzo[b]furan

(96) 3-(4-Methylsulfonyl)phenyl)-2-phenylbenzo[b]thiophene

(97) 3-(4-Methylsulfonyl)phenyl-2-phenylinden-1-one

(98) 2-(4-Fluorophenyl)-3-(4-(methylsulfonyl)phenyl)indole

(99) 3-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)indole

(100) 2-(4-Fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-4H-thieno[2,3-c]-furan-6-one

(101) 2-(3,4-Difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-4H-thieno[2,3-c]-furan-6-one

(102) 2-(4-Fluorophenyl)-3-(4-(aminosulfonyl)phenyl)-4H-thieno[2,3-c]-furan-6-one

(103) 2-(3,4-Difluorophenyl)-3-(4-(aminosulfonyl)phenyl)-4H-thieno[2,3-c]-furan-6-one

(104) 3-(4-(Methylsulfonyl)phenyl)-2-phenyl)-4,7-dihydrothieno[2,3-c]pyran-5-one

(105) 2-(4-(Methylsulfonyl)phenyl)-3-phenyl)-4H-thieno[2,3-c]furan-6-one

(106) 5-(4-(Methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b] thiazole

(107) 2-Methyl-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo [2,1-b]thiazole

(108) 3-Methyl-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo [2,1-b]thiazole

(109) 2-Bromo-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo [2,1-b]thiazole

(110) 3-Trifluoromethyl-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole

(111) 2,3-Dimethyl-5-(4-(methylsulfonyl)phenyl)-6-phenyl-imidazo[2,1-b]thiazole

(112) 5-(4-(Methylsulfonyl)phenyl)-6-(4-fluorophenyl) imidazo[2,1-b]thiazole

(113) 5-Phenyl)-6-(4-(methylsulfonyl)phenyl)-imidazo[2,1-b]thiazole

(114) 2-Chloro-5-(4-(methylsulfonyl)phenyl)-6-(4-chlorophenyl)imidazo[2,1-b]thiazole

(115) 2,2-Dichloro-5-(4-(methylsulfonyl)phenyl)-6-(4-chlorophenyl)imidazo[2,1-b]thiazole

(116) 5-(4-(Methylsulfonyl)phenyl)-6-(imidazo[2,1-b]-1,3,4-thiadiazole

(117) 5-Phenyl-6-(4-(methylsulfonyl)phenyl)-imidazo[2,1-b]-1,3,4-thiadiazole

(118) 2-Methyl-5-(4-(methylsulfonyl)phenyl)-6-phenyl-imidazo[2,1-b]-1,3,4-thiadiazole

(119) 2-Methyl-5-phenyl-6-(4-methylsulfonyl)phenyl)-imidazo[2,1-b]-1,3,4-thiadiazole

(120) 5-(4-(Methylsulfonyl)phenyl)-6-(4-fluorophenyl)-imidazo[2,1-b]-1,3,4-thiadiazole

(121) 5-(4-(Methylsulfonyl)phenyl)-6-phenyl-1H-imidazo[2,1-b]-s-triazole

(122) 5-Phenyl-6-(4-(methylsulfonyl)phenyl)thiazolo[3,2-b]-1,3,4-triazole

(123) 2,3-Dihydro-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole

(124) 2-[(4-Methylthio)phenyl]-1-biphenyl

(125) 1-Cyclohexene-2-(4'-methylsulfonylphenyl)benzene

(126) 3-(4'-Methylsulfonylphenyl)-4-phenylphenol

(127) 1-[2-(4-Methylsulfonylphenyl)phenyl]piperidine

(128) 1-[2-(4'-Methylsulfonylphenyl)phenyl]pyrrole

(129) 1-Phenoxy-2-(4'-methylsulfonylphenyl)benzene

(130) 5-(4-Fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine

(131) 2-Ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine

(132) 5-(4-Fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine

(133) 2-Bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine

(134) 3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]propanoic acid

(135) 3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]butanoic acid, sodium salt

(136) 2-Benzyl-3-[1-(p-bromobenzyl)-5-methoxy-2-methylindol-3-yl-propanoic acid

(137) 3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]-2,2-dimethylpropanoic acid

(138) 3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]-4,4,4-trifluorobutanoic acid, sodium salt

(139) trans-2-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]-cyclopropanecarboxylic acid, sodium salt

(140) 3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]-hydroxy-2-methyl propanoic acid, sodium salt

(141) [1-(1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]-cyclopropylacetic acid, sodium salt

(142) trans-(+)-2-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]cyclopropanecarboxylic acid, sodium salt

(143) 3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]-2-methylpropanoic acid and sodium salt

(144) 3-[1-(p-Chlorobenzyl)-5-methoxy-2-methylindol-3-yl]-4,4,4-trifluorobutanoic acid and sodium salt

(145) syn-3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]-2-methylbutanoic acid

(146) anti-3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]-2-methylbutanoic acid and sodium salt

(147) 3-[5-(Bromo-1-(p-bromobenzyl)-2-methylindol-3-yl]butanoic acid and sodium salt

(148) (—)-3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]-butanoic acid and sodium salt

(149) (+)-3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]-butanoic acid and sodium salt

(150) trans-(—)-2-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl]cyclopropanecarboxylic acid and sodium salt

(151) 3-[1-(p-Bromobenzyl)-2,5-dimethylindol-3-yl]propanoic acid

(152) 3-[5-(Bromo-1-(p-bromobenzyl)-2-methylindol-3-yl]propanoic acid

(153) 3-[1-(p-Bromobenzyl)-5-chloro-2-methylindol-3-yl)propanoic acid

(154) 3-[1-(p-Chlorobenzyl)-5-methoxy-2-methylindol-3-yl)-2-methylpropanoic acid

(155) Methyl 3-[1-(p-bromobenzyl)-5-methoxy-2-methylindol-3-yl)propanoate

(156) 3-[1-(p-Bromobenzyl)-5-methoxy-2-methylindol-3-yl)-3-methylbutanoic acid

(157) 5-Methanesulfonamido-6-(2,4-difluorophenylthio)-1-indanone

(158) 5-Methanesulfonamido-6-(2,4-dichlorophenoxy)-1-indanone

(159) 2-(4-Chlorophenyl)-4-hydroxy-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazole

(160) 2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole

(161) 1-(4-Fluorophenyl)-4-hydroxy-2-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-4,5-dihydro-1H-imidazole

(162) 1-(4-Fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole

(163) 2-(4-Chlorophenyl)-1-[4-methylsulfonyl)phenyl]-4-methyl-1H-imidazole

(164) 2-(4-Chlorophenyl)-1-[4-methylsulfonyl)phenyl]-4-phenyl-1H-imidazole

(165) 2-(4-Chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

(166) 4-(4-Bromophenyl)-2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

(167) 2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(2-naphthyl)-1H-imidazole

(168) 2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-[4-(trifluoromethoxy)phenyl]-1H-imidazole

(169) 2,4-Bis(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

(170) 2-(4-Chlorophenyl)-4-(3-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

(171) 2-(4-Chlorophenyl)-4-(4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

(172) 2-(4-Chlorophenyl)-4-(3-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

(173) 2-(4-Chlorophenyl)-4-[(4-chlorophenoxy)methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

(174) 2-(3-Chloro-4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole

(175) 5-[1-[4-(Methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazole-2-yl]-1,3-benzodioxole

(176) 2-(3-Fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)-phenyl-4-(trifluoromethyl)-1H-imidazole

(177) 2-(4-Chlorophenyl)-4-[(phenylthio)methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

(178) 2-(4-Chlorophenyl)-4-[(N-methyl-N-phenylamino)methyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

(179) 2-(4-Chlorophenyl)-4-[2-quinolyl)methoxymethyl]-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

(180) 2-(4-Chlorophenyl)-4-methoxymethyl-1-[4-(methylsulfonyl)phenyl]-1H-imidazole

(181) 2-(4-Fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole

(182) 1-[4-(Methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole

(183) 2-(3-Chloro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole

(184) 2-(4-Methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole

(185) 1-[4-(Methylsulfonyl)phenyl]-2-(4-trifluoromethyl-phenyl)-4-trifluomethyl-1H-imidazole

(186) 4-[2-(4-Chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide

(187) 4-[2-(3-Chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide

(188) 3-[1-(4-Methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

(189) 2-[1-(4-Methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

(190) 4-[1-[4-(Methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

(191) 2-Methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

(192) 2-Methyl-6-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

(193) 5-Methyl-2-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

(194) 4-Methyl-2-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

(195) 2-Methoxy-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine

(196) 4-[2-(6-Methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide

(197) 4-[2-(6-Methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide

(198) 3-Methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine

(199) 4-[2-(4-Methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide

(200) 2-[1-[4-(Methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]thiophene

(201) 3-[1-[4-(Methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]thiophene

(202) 4-[2-(5-Methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide

(203) 2-Methyl-3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]thiophene

(204) 4-[2-(2-Methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide

(205) 4-[2-Pyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide

The synthesis of compounds 1-39 is disclosed in Talley et al. U.S. Patent No. 5,466,823. The synthesis of compounds 40 and 41 is disclosed in Black et al.

U.S. Patent No. 5,436,265. The synthesis of compounds 42-94 is disclosed in Ducharme et al. U.S. Patent No. 5,474,995. The synthesis of compounds 95-105 is disclosed in Prasit et al. U.S. Patent No. 5,521,213. The synthesis of compounds 106-123 is disclosed in Gauthier et al. U.S. Patent No. 5,552,422. The synthesis of compounds 124-129 is disclosed in Batt U.S. Patent No. 5,593,994. The synthesis of compounds 130-133 is disclosed in Lee U.S. Patent No. 5,596,008. The synthesis of compounds 134-156 is disclosed in Lau et al. U.S. Patent No. 5,604,253. The synthesis of compounds 157 and 158 is disclosed in Guay et al. U.S. Patent No. 5,604,260. The synthesis of compounds 159-205 is disclosed in Khanna et al. U.S. Patent No. 5,616,601.

Other selective inhibitors of cyclooxygenase-2 and their synthesis are taught in Examples 2-108, 110-129, 131-150, 152, 301-312, and 401-413 of Batt et al. U.S. Patent No. 5,593,994, the disclosure of which is incorporated herein by reference. Still other selective inhibitors of cyclooxygenase-2 and their synthesis are taught in Examples 1-11, 13-16, and 18-25 of Guay et al. U.S. Patent No. 5,604,260, the disclosure of which is incorporated herein by reference. Still other selective inhibitors of cyclooxygenase-2 and their synthesis are taught in Examples 1-13 including Examples 1a-1p and 4a-4h of Talley et al. U.S. Patent No. 5,633,272, the disclosure of which is incorporated herein by reference. Still other selective inhibitors of cyclooxygenase-2 are taught in Examples 1-131 of Lau et al. U.S. Patent No. 5,639,780, the disclosure of which is incorporated herein by reference. Still other selective inhibitors of cyclooxygenase-2 are taught in Examples 1-6 of Talley et al. U.S. Patent No. 5,643,933, the disclosure of which is incorporated herein by reference. Still other selective inhibitors of cyclooxygenase-2 are taught in Examples 1-4 of Lau et al. U.S. Patent No. 5,510,368, the disclosure of which is incorporated herein by reference.

Preferred inhibitors of cyclooxygenase-2 for use herein are 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide which is compound (1) set forth above and 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide which is compound (4) set forth above; it is believed the latter compound is celicoxib (Trade name Celebrex). Another preferred

selective inhibitor of cyclooxygenase-2 is vioxx which is MK-0966. Other preferred inhibitors of cyclooxygenase-2 for use in this embodiment are those described hereinafter in connection with the third embodiment herein.

The dosage of inhibitor of cyclooxygenase-2 for the method of the first embodiment herein is a cyclooxygenase-2 inhibiting amount which is a therapeutically effective amount. In general, the dosage for the first embodiment herein ranges from 0.1 to 30 mg/kg. The dosages for any particular agent will vary within said range. For compound (1) referred to above, the dosage preferably ranges from 3 to 12 mg/kg. The administration is preferably chronic treatment, i.e., carried out indefinitely.

The route of administration for the inhibitors of cyclooxygenase-2 for the first embodiment herein is preferably oral but other routes of administration, e.g., parenteral such as intravenous, are also useful.

We turn now to the second embodiment herein, which is a method of treating a patient with a virus-caused liver disease with a cyclooxygenase-2 inhibiting amount of a selective inhibitor of cyclooxygenase-2 and a therapeutic amount of an anti-viral drug where the cyclooxygenase-2 inhibitor is an adjunct to the anti-viral therapy to increase the effectiveness thereof.

For the second embodiment herein, the virus-cause liver diseases include, for example, chronic viral hepatitis B and chronic viral hepatitis C.

For the second embodiment herein, the inhibitors of cyclooxygenase-2 that are useful are the same as those for the first embodiment herein and the dosage regimen and routes of administration are the same as for the first embodiment.

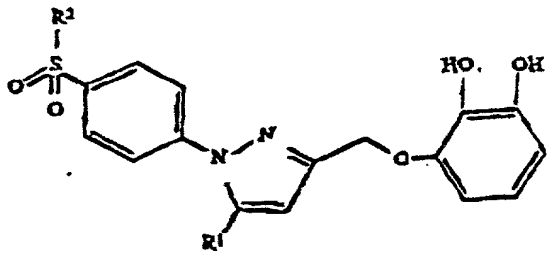
The anti-viral drugs are the same as those used conventionally for the disorder treated, and the dosages and routes of administration are those conventional for the disorder treated. For example, for chronic hepatitis B, various interferons, e.g., recombinant and natural alpha interferons, are administered parenterally and for chronic hepatitis C, interferon alpha-2b is administered subcutaneously (3MU three times a week for six months). Other anti-viral compounds for use in the second embodiment herein include, for example, acyclovir, adenine arabinoside, and ribavirin, used, for example in conventional dosages. Combinations of agents, e.g., a

combination of interferon and ribavirin, may be used with the selective inhibitor of cyclooxygenase-2.

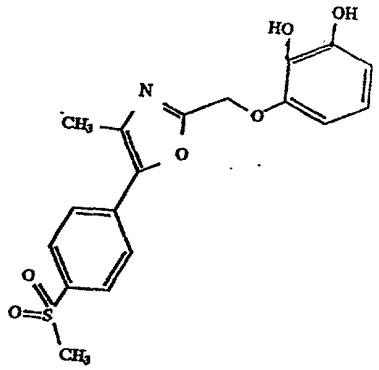
We turn now to the third embodiment herein which is directed to selective inhibitors of cyclooxygenase-2 which directly inhibit the enzyme cyclooxygenase-2 and which also inhibit the synthesis of cyclooxygenase-2 protein and which have antioxidant properties.

The cyclooxygenase-2 inhibitors for this third embodiment preferably contain phenyl group with two or more substituents selected from the group consisting of hydroxy and C_{1-4}-alkoxy (e.g., methoxy) on the phenyl. Such compounds are embraced by generic description in various patents but no species of selective cyclooxygenase-2 inhibitor containing phenyl group with two or more hydroxy or alkoxy substituents is disclosed in any of said patents. The patents referred to are: Talley et al. U.S. Patent No. 5,643,933; Talley et al. U.S. Patent No. 5,633,272; Khanna et al. U.S. Patent No. 5,616,601; Lee U.S. Patent No. 5,596,008; Batt et al. U.S. Patent No. 5,593,994; and Adams et al. U.S. Patent No. 5,593,992.

Specific compounds for the third embodiment herein include, for example, 4-[5-methyl-3-[[(2,3-hydroxy)phenoxy]methyl]-1H-pyrazol-1-yl]benzenesulfonamide and 4-methyl-5-(4-methylsulfonyl)phenyl-2-[(2,3-hydroxyphenoxy)methyl]oxazole and the corresponding compounds where methoxy or ethoxy replaces hydroxy. 4-[5-Methyl-3-[[(2,3-hydroxy)phenoxy]methyl]-1H-pyrazol-1-yl]benzenesulfonamide has the structure



where R^1 is methyl and R_2 is NH_2. 4-(Methyl)-5-(4-methylsulfonyl)phenyl-2-[(2,3-hydroxyphenoxy)methyl]oxazole has the structure



These compounds are embraced by broad disclosure in Talley et al. U.S. Patent No. 5,643,933 but are not specifically disclosed therein. These compounds can be made analogously to Scheme XXII in U.S. Patent No. 5,643,933 by reacting 2,3-dihydroxybenzyl bromide, where the hydroxy groups are protected by conventional techniques (for example, as described in E. Haslam, "Protection of Phenols and Catechols", pages 145-182 in Protective Groups in Organic Chemistry, McOmie, J. F. W., editor, Plenum Press, London (1973), with alcohol corresponding to the product sought, in the presence of base, and deprotecting, and in the case of the methoxy or ethoxy compounds with alkoxy substituents in phenyl moiety, replacing the hydroxy substituents with alkoxy. Alternatively, these compounds can be made by reacting said alcohol with mesyl chloride to yield the unstable mesylate and then reacting with appropriate trihydroxyphenol. These compounds directly inhibit the cyclooxygenase-2 enzyme and also inhibit the synthesis of cyclooxygenase-2.

The selective inhibitors of cyclooxygenase-2 for the third embodiment herein have utility as broad spectrum anti-inflammatory agents for treating inflammation and inflammation-associated disorders mediated by cyclooxygenase-2 such as arthritis, inflammatory bowel disease, diabetes, Alzheimer's disease, pancreatitis, inflammatory vascular and ocular disorders, and liver disease (as described in conjunction with the first embodiment herein). They also have utility in preventing or treating cancer. The dosages are generally those set forth for selective inhibitors of cyclooxygenase-2 in the first embodiment herein. The route of administration is preferably oral although other routes of administration, e.g., parenteral, such as intravenous, may also be used.

The selective inhibitors of cyclooxygenase-2 of the third embodiment herein have improved anti-inflammatory efficacy compared to selective inhibitors of cyclooxygenase-2 which do not inhibit the synthesis of cyclooxygenase-2 protein.

The three embodiments described above are illustrated in the following examples.

EXAMPLE I

A patient with alcoholic hepatitis is admitted to a hospital complaining of nausea and upper abdominal pain. Liver function test results are total bilirubin of 4.0 mg/dl, direct bilirubin of 3.1 mg/dl, ALT of 100 IU/L, AST of 120 IU/L and prothrombin time of 15.1 seconds.

Treatment is carried out by administration of 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide at a dosage of 6 mg/kg by oral route of administration, daily.

At the end of three weeks, the nausea and upper abdominal pain have resolved. Each of the blood tests has improved.

The same result is obtained when the drug administered is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide at a dosage of 6 mg/kg by oral route of administration daily.

EXAMPLE II

The patient is a 45-year old female with new onset nausea, loss of appetite and right upper quadrant tenderness. She is noted to have elevated liver chemistries. Serologic workup is notable for positive antinuclear and antismooth muscle antibodies. She is considered to have autoimmune hepatitis. Liver biopsy is consistent with this diagnosis. Treatments with 6 mg/kg oral 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzene-sulfonamide for two months, results in resolution of symptoms. The patient is subsequently maintained on an oral dose of 6 mg/kg of the same drug.

The same result is obtained when the drug administered is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide at an oral dose of 6 mg/kg.

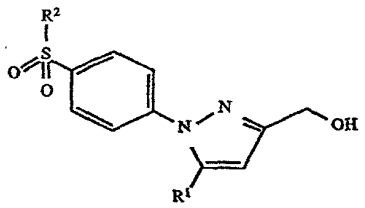
EXAMPLE III

A patient having symptoms of malaise, anorexia and fatigue, has persistently elevated liver function tests. A blood test confirms the diagnosis of chronic viral hepatitis C.

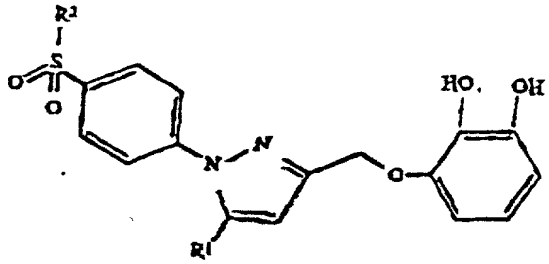
The patient is treated by oral administration of 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzene-sulfonamide at a dose of 6 mg/kg, daily for 12 months and also with subcutaneous interferon alpha-2b at a dose of 3MU three times a week for six months, resulting in sustained normalization of liver enzymes.

The same result is obtained when the cyclooxygenase-2 inhibitor is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide at an oral dose of 6 mg/kg and the anti-viral drug is subcutaneous interferon alpha-2b at a dose of 3 Mu three times a week for six months.

EXAMPLE IV



where R^1 is methyl and R^2 is NH_2 is reacted with 2,3-dihydroxybenzylbromide where the hydroxyls are protected, under basic conditions (K_2CO_3), and then deprotecting is carried out to produce 4-[5-methyl-3-[(2,3-hydroxy)phenoxy]methyl]-1H-pyrazol-1-yl]benzenesulfonamide. The product has the structure



where R^1 is methyl and R^2 is NH_2. The starting material is made by the reaction to produce compound 78 in Scheme XVII depicted in Talley et al. U.S. Patent No. 5,643,933.

Many variations of the above will be obvious to those skilled in the art. Thus, the invention is defined by the claims.

WHAT IS CLAIMED IS:

1. A method of treating a patient with liver disease comprising administering to said patient a cyclooxygenase-2 inhibiting amount of a selective inhibitor of cyclooxygenase-2.

2. The method of Claim 1, wherein the liver disease is an inflammatory liver disorder.

3. The method of Claim 2, wherein the inflammatory liver disorder is selected from the group consisting of chronic viral hepatitis B, chronic viral hepatitis C, alcoholic liver injury, primary biliary cirrhosis, autoimmune hepatitis, nonalcoholic steatohepatitis, and liver transplant rejection.

4. The method of Claim 3, wherein the selective inhibitor of cyclooxygenase-2 is 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

5. The method of Claim 3, wherein the selective inhibitor of cyclooxygenase-2 is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

6. The method of Claim 3, wherein the selective inhibitor of cyclooxygenase-2 directly inhibits the enzyme cyclooxygenase-2 and also inhibits the synthesis of cyclooxygenase-2 protein.

7. A method of treating a patient with a virus-caused liver disease comprising administering to said patient a cyclooxygenase-2 inhibiting amount of selective inhibitor of cyclooxygenase-2 and therapeutic amount(s) of anti-viral drug(s).

8. The method of Claim 7, wherein the liver disease is selected from the group consisting of chronic viral hepatitis B and chronic viral hepatitis C.

9. The method of Claim 8, wherein the selective inhibitor of cyclooxygenase-2 is 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

10. The method of Claim 8, wherein the selective inhibitor of cyclooxygenase-2 is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

11. The method of Claim 8, wherein the selective inhibitor of cyclooxygenase-2 directly inhibits the enzyme cyclooxygenase-2 and also inhibits the synthesis of cyclooxygenase- protein.

12. A selective inhibitor of cyclooxygenase-2 which directly inhibits the enzyme cyclooxygenase-2 and which also inhibits the synthesis of cyclooxygenase-2 protein.

13. The selective inhibitor of cyclooxygenase-2 of Claim 12 which contains phenyl group with two or more substituents on the phenyl group selected from the group consisting of hydroxy and C_{1-4}-alkoxy.

14. The selective inhibitor of Claim 13 which is selected from the group consisting of 4-[5-(4-methyl-3-[[(2,3-hydroxy)phenoxy]methyl]-1H-pyrazol-1-yl]benzenesulfonamide and 4-methyl-5-(4-methylsulfonyl)phenyl-2-[(2,3-hydroxyphenoxy)methyl]oxazole and the corresponding compounds where methoxy or ethoxy replace hydroxy.

15. The selective inhibitor of cyclooxygenase-2 of Claim 14 which is 4-[5-methyl-3-[[(2,3-hydroxy)phenoxy]methyl]-1H-pyrazol-1-yl]benzenesulfonamide.

16. The selective inhibitor of cyclooxygenase-2 of Claim 14 which is 4-methyl-5-(4-methylsulfonyl)phenyl-2-[(2,3-hydroxyphenoxy) methyl]oxazole.

CYCLOOXYGENASE-2 INHIBITION

Abstract of the Disclosure

Selective inhibitors of cyclooxygenase-2 are used to treat liver disease and in combination with anti-viral drugs to treat virus-caused liver disorders. Selective inhibitors of cyclooxygenase-2 which also inhibit the synthesis of cyclooxygenase-2 improve over the efficacy of conventional selective inhibitors of cyclooxygenase-2 in the treatment of inflammatory conditions, Alzheimer's disease and cancer.

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

This declaration is of the following type:

[ ] original
[ ] design
[ ] supplemental
[X] national stage of PCT
[ ] divisional
[ ] continuation
[ ] continuation-in-part (CIP)

My residence, post office address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed for and for which a patent is sought on the invention entitled:

CYCLOOXYGENASE-2 INHIBITION

the specification of which

[ ] is attached hereto
[ ] was filed on _____, as
Application No. _____
and was amended on _____
(if applicable)
[X] was described and claimed in PCT International Application No. PCT/US98/25206
filed on 7 December 1998 and as amended under PCT Article 19 on _____ (if any).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any Amendment referred to above.

I acknowledge duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

[ ] In compliance with this duty there is attached an Information Disclosure Statement. 37 CFR 1.97.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119, of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent of inventor's certificate having a filing date before that of the application on which priority is claimed:

[ ] no such applications have been filed
[ ] such applications have been filed as follows.

Prior Foreign Application(s)

(Number)	(Country)	(day/month/year filed)	[ ] [ ] Yes No
(Number)	(Country)	(day/month/year filed)	[ ] [ ] Yes No

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

60/069,955 (Application Number)	17 December 1997 (Filing Date)
(Application Number)	(Filing Date)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below, and insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose all information known to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application No.)	(Filing Date)	(patented, pending, abandoned)
(Application No.)	(Filing Date)	(patented, pending, abandoned)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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I hereby declare all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor ANDREW I. DANNENBERG

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